

Progress report

Dietary lactose and the aetiology of human small-intestinal hypolactasia

The only carbohydrate in milk is lactose, a disaccharide, which is formed of a molecule of glucose and a molecule of galactose. Cow's milk contains about 5% lactose and human milk about 6.5-7%. Lactose is hydrolysed to its monosaccharides principally by a specific enzyme, lactase, which is a β -galactosidase. There are also two other enzymes with β -galactosidase activity, lysosomal acid β -galactosidase and cytoplasmic hetero- β -galactosidase, but their role in the hydrolysis of lactose is very small¹. The latter has only *in vitro* activity.

Historical development

LOCATION OF LACTASE ENZYME

It has been known for a long time that milk may produce loose stools or even diarrhoea in some people and therefore many populations considered milk unsuitable for consumption after weaning². Over 100 years ago it was observed that milk sugar (lactose) produced diarrhoea to the dog³. The pathophysiological mechanism of this condition was elucidated in 1903 by Röhmann and Nagano⁴, who found in dogs that unhydrolysed lactose molecules remained in the lumen of the small intestine for some time producing a strong osmotic effect and diarrhoea. Lactose remained unhydrolysed because very little lactase activity existed in the small intestine. This observation was confirmed later in humans by more sophisticated methods⁵⁻⁷.

Soon after the first observations of lactase activity in the small intestine in the 1890s^{8,9} it was found that, in general, it was possible to demonstrate activity only in young animals¹⁰⁻¹², although some authors found lactase activity also in old animals¹³. The principal site of activity seemed to be the small-intestinal mucosa^{11,14-17}, activity being highest in the jejunum and decreasing toward the ileum. Controversy existed over lactase activity in the small-intestinal juice, succus entericus. Some authors found activity¹⁸, while others did not^{4,19}. Although in some studies²⁰, especially in those by Cajori in 1933²¹ and in 1935²², it appeared evident that lactose was hydrolysed in the small-intestinal epithelium and only insignificant amounts of activity existed in the succus entericus, many later textbooks stated that the only site of lactase enzyme was the intestinal juice²³⁻²⁶. It was not until the late 1950s and early 1960s with the publications of Borgström *et al.*²⁷ and Dahlqvist *et al.*²⁸ that it became generally accepted that the hydrolysis of lactose takes place in the outer membrane of the mucosal epithelial cells and not in the small intestinal juice, where lactase activity is very low and of no functional importance.

ANIMAL FEEDING EXPERIMENTS

Feeding experiments concerning the possibility of affecting the intestinal activity of lactase were carried out soon after the discovery of lactase. Animals were fed lactose for periods ranging from a few days to a few months. Generally, no change in lactase activity was found^{11,17}, although opposite results were also presented¹³.

In 1896 Fischer and Niebel¹⁵ doubted that lactase adaptation took place in old animals after a long feeding of milk but they could not prove this. Weinland demonstrated in 1899¹³ that milk consumption of several months produced lactase activity in rabbits after the suckling period. Most authors indicated, however, that lactose feeding could not provoke lactase activity in the animal small intestine. Orban fed rabbits for four days¹¹, and in 1906 Plimmer¹⁷ reported the results of thorough long-lasting experiments in rabbits, rats, and other animals. Both authors concluded that no adaptation occurs. Bainbridge²⁹ also showed no increase in lactase activity in the small intestine of dogs, but he agreed with Weinland's view that lactose feeding will provoke lactase activity in the pancreas. This was later proved to be incorrect¹⁷.

After these early feeding experiments no new work was reported until, in 1949, Fischer *et al.* concluded that no adaptive change in lactase activity exists³⁰ and Heilskov in 1951³¹ showed that lactose feeding of rabbits did not prevent the normal decline of lactase activity after weaning. In 1957 Fischer reported interesting findings³². She found a 50% increase in lactase activity in rats fed lactose, but at the same time she found an increase in the total nitrogen in the small-intestinal mucous membrane of these animals. The increase in the enzyme activity per unit of tissue nitrogen was not significantly higher in the lactose-fed category compared with the change in the reference category. She concluded that the change in lactase activity did not satisfy conservative criteria of substrate-induced enzymatic adaptation and considered her findings to be an example of metabolic adaptation. Other experiments carried out before 1964 reported no adaptation³³⁻³⁵.

HUMAN LACTASE

At the end of the last century and at the beginning of this century there were only a few observations of lactase activity in the small intestine of children^{14,36}. Activity was found during infancy, but it was strongly reduced by severe diseases¹⁴. No feeding experiments were done.

The malabsorption of lactose was not known to be of any clinical importance in man. However, early this century attention was paid to the diarrhoea that lactose occasionally caused in infants^{37,38}. In 1921 Howland stated that 'there is with many patients an abnormal response on the part of the intestine to carbohydrates, which expresses itself in the form of diarrhoea and excessive fermentation. Such patients may have some deficit in the ferments necessary for the hydrolysis of lactose'³⁹. It is possible that the cause of diarrhoea mentioned by these paediatricians was not lactose malabsorption. However, no studies concerning the effects of dietary lactose in children or human adults were done for many years.

HYPOLACTASIA IN MAN

In 1959 Holzel *et al.*⁴⁰ described two siblings who had watery diarrhoea from birth and a very low lactase activity in the small intestine. Diarrhoea was

induced by unabsorbed lactose. Subsequently, a few more such infants and children with congenital hypolactasia have been recorded⁴¹⁻⁴².

In 1963 Auricchio *et al.*⁴³ and Dahlqvist *et al.*⁴⁴ independently described adults with a low lactase activity which, on the evidence of the case history, was not congenitally low but had decreased since birth as in animals. These and later observations have dispelled the view that lactase activity remains high in man throughout life. On the contrary, selective adult hypolactasia is prevalent in adulthood in the greater part of mankind⁴⁵⁻⁵⁰. The areas where hypolactasia exists parallel the areas where adults consume no milk and *vice versa*^{46-47, 49-50}. The age at which adult hypolactasia manifests itself ranges from 1 to 2 years⁵¹⁻⁵² to 20 years⁵³⁻⁵⁵.

This phenomenon has clinical and nutritional significance, because people with hypolactasia (lactose malabsorption) usually suffer from abdominal symptoms when they drink milk: meteorism, borborygmi, abdominal fullness, loose stools or diarrhoea, and sometimes abdominal pain⁵⁵⁻⁵⁹. The severity of symptoms varies from person to person, some people getting symptoms from a very small amount of lactose⁵⁷, while others, especially children, tolerate more^{52, 60}. Increasing attention has been paid to the possibility that milk and milk powder is a harmful nutrient to children in developing countries, because the prevalence of selective hypolactasia in those countries is already very high at the age of 5 years—for example, in Thailand it is 90-100%^{52, 61} and in many Negro tribes in Africa over 70%^{51, 62-63}. There has been a lot of discussion as to whether the possible diarrhoea produced by milk could be severe enough to cause malabsorption of other milk constituents in these children⁶⁴⁻⁷¹ and whether it can make the former slight malnutrition worse in circumstances of inadequate nutrition and hygiene⁷².

Terminology and diagnosis of hypolactasia

The terminology used in discussing this disorder has been confusing. It is suggested that the correct terminology should be as follows. *Hypolactasia* means a very low activity of lactase in the jejunal mucosa and this has been determined by a direct assay of lactase—for example, from a jejunal biopsy sample^{41, 73}. *Lactase deficiency* implies a total lack of lactase activity, which perhaps never happens even in the case of the congenital disorder when lactase activity is generally much lower than in the adult type⁷⁴. The limit between hypolactasia and moderate lactase activity in people with *lactase persistence* is arbitrary and differs a little between laboratories. However, the distribution of lactase activity values is bimodal. Despite a certain amount of overlapping the cases with hypolactasia can be identified quite reliably⁷⁵.

Because it is inconvenient to take small intestinal biopsies for lactase activity determinations, a lactose loading (tolerance) test has been developed to verify hypolactasia or, in fact, the ability of the small intestinal mucosa to hydrolyse and absorb lactose. Usually 50 g of lactose, or 1.0 g/kg of body weight, are given by mouth and capillary blood samples are taken for the determination of glucose concentration from the fasting level up to 60 minutes after the lactose^{73, 76-77}. A maximum rise of 1.1 mmol/l (20 mg/100 ml) above the fasting level is universally agreed to be the upper limit of lactose malabsorption and this correlates well with the state of hypolactasia^{58, 73, 78-79}. However, false positive and negative results also exist^{58, 73, 80}.

To improve the validity of the lactose loading test measuring the rise in the

blood galactose concentration has been used in addition to the rise in blood glucose^{79,81-82}. It is necessary to give a small amount of alcohol before the lactose load to inhibit the rapid metabolism of galactose. The upper limit of the galactose rise in people with hypolactasia has been found to be 0.3 mmol/l (5 mg/100 ml)^{54,83-85}. The sensitivity and specificity of the lactose loading test with ethanol is considerably better than if only blood glucose were determined⁵⁴. The modification where only blood galactose is determined is simpler and also reliable^{83,85}.

The concentration of hydrogen in the expired breath also reflects very well the activity of lactase⁸⁶⁻⁸⁸. Unabsorbed lactose splits in the colon to lactic acid, hydrogen, and CO₂. A portion of the H₂ diffuses into the circulation and through the lungs. It can be detected in the breath. The sensitivity and specificity of the breath hydrogen test may be even higher than that of the lactose loading test with ethanol⁸⁷.

The term *lactose malabsorption* (or *maldigestion*) means a low rise in blood glucose or in blood glucose and galactose concentration in the lactose loading test. It almost always implies hypolactasia, often making these terms interchangeable. In the literature the term *lactose intolerance* is also often used to mean the same thing, because subjects with lactose malabsorption generally do not tolerate lactose, but have abdominal symptoms because of it. However, some people with lactose malabsorption have no symptoms and there are people who cannot tolerate lactose, although lactose is hydrolysed and absorbed^{54,78,82}. Therefore the term lactose intolerance should be avoided when speaking about lactose malabsorption.

The term *milk intolerance* means that a person gets abdominal symptoms after milk ingestion, but very often this does not mean that the cause is lactose malabsorption.

Jejunal hypolactasia and lactose malabsorption may appear secondarily during infection or infestation of the small intestine, in protein joule malnutrition or kwashiorkor⁸⁹⁻⁹¹. In these cases the histological structure of the intestine is often abnormal. Secondary decrease in lactase activity should be clearly separated from the primary and selective one, when the histological structure of the mucosa and the activities of other disaccharidases are quite normal.

Aetiology of hypolactasia

HYPOTHESES

The aetiology of the decline in lactase activity to a very low level after infancy was unclear for a long time. Causes proposed for selective adult hypolactasia were⁹²: (1) genetic inheritance, (2) stopping milk (lactose) consumption, (3) ageing, (4) the cases found were the lowest values of the 'normal' lactase level, (5) an acquired enzyme inhibitor, (6) a transitory small bowel disease. The last possibility was known to be real, but almost always this led to malabsorption of other disaccharides, too; hypolactasia was not selective. No natural enzyme inhibitor was found⁷⁸ and, because quite young people developed it and, in addition, the distribution of lactase activity values seemed to be bimodal, the two first causes remained most likely.

The genetic hypothesis was credible, because congenital disaccharidase defects were also hereditary⁴¹⁻⁴². It was also supported by the observation that, in different races and populations, even in neighbouring tribes, the

prevalence of selective hypolactasia varied considerably^{45, 62, 93}. On the other hand, this was also used as an argument for the adaptive aetiology of hypolactasia, because populations which had a high prevalence of hypolactasia consumed little milk in adulthood and *vice versa*⁹⁴⁻⁹⁶. The supporters of the adaptive hypothesis considered that abundant milk consumption maintained high lactase activity and that the lack of milk in the diet reduced it and caused hypolactasia to develop in children who no longer drank milk after weaning⁹¹. The proponents of the genetic hypothesis thought that some selecting factors associated with milk consumption had continued for thousands of years and produced the differences in the present prevalence rates of selective hypolactasia⁴⁶⁻⁴⁷. So, the ability to hydrolyse and absorb lactose led to higher and higher milk consumption in people who could also use all the nutrients in the milk without diarrhoea and were therefore better fitted to survive than those with hypolactasia. In areas where there had been no domestication of dairy animals, and therefore no milk consumption in adults, as in many parts of Africa and Asia, this selection mechanism had no influence; the inherited decline of lactase activity after weaning predominated in these areas as it does in mammals.

It seemed important to understand the aetiology of the decline in lactase activity, because of the high worldwide prevalence of lactose malabsorption and its importance in the field of public health. If the decline were caused by the lack of a substrate (lactose) in the food of children, it would be much easier to organise and give reasons for nutrition programmes—for example, in developing countries using milk as a protein source. People with hypolactasia would probably become symptomless just by continuing to drink milk. If the aetiology were genetic, nutrition programmes in developing countries ought to be arranged differently.

ANIMAL FEEDING EXPERIMENTS

In the 1960s Dahlqvist developed an enzymatic method for intestinal disaccharidase determinations that was more accurate than the previously used reduction method⁹⁷⁻⁹⁸. The new method could reliably find smaller amounts and changes in lactase activity.

After this method was developed, several studies reported an adaptive change in jejunal lactase activity. In 1964 Girardet *et al.*⁹⁹ found an increase in lactase activity in rats after six to nine weeks when fed 25% lactose in the diet, and Huber *et al.*¹⁰⁰ found similar results in 24 calves fed increasing amounts of lactose for 11 weeks. Cain *et al.*¹⁰¹ fed a diet containing as much as 60% lactose and found after five to seven weeks an adaptation in rats. Bolin *et al.*^{102, 103} found the same using 30% of lactose in the diet. Broitman *et al.*¹⁰⁴ and Reddy *et al.*¹⁰⁵ reported similar findings. These changes in lactase activity, an increase of about 50% and a decrease of less than 40% (17), were, however, small compared with the postweaning decline in lactase activity^{34-35, 102}. Since the differences in lactase activity of old and infant animals were about 10-fold³⁴, one would expect big differences also in feeding experiments if lactase were adaptive.

In many other studies no adaptation could be demonstrated, although rats¹⁰⁶⁻¹¹¹, calves¹¹², or pigs¹¹³⁻¹¹⁴ were used as experimental animals. Wen *et al.*¹¹⁵ reported an adaptation of lactase after four months of lactose diet in some monkey species, while in other species no adaptation could be demonstrated. Ferguson *et al.*¹¹⁶ implanted isografts of fetal mouse intestine into

adult mice and demonstrated that the implanted mouse intestine developed the same kind of lactase pattern as the normal mouse intestine does after birth, although it was never exposed to food. In no study was lactose feeding able to prevent the normal postweaning decline of lactase activity^{34,102,109}. However, it seemed possible that the decline might start later in animals given lactose continuously after weaning than in those deprived of lactose¹⁰³. In 18 to 26-day-old rats in the former category, the level of activity was a little higher¹⁰⁹.

In addition, the effect of lactose was found to be non-specific, in that lactose rich and lactose deficient diets also affected the sucrase and maltase levels¹⁰². In addition, glucose feeding caused lactase activity to increase.

HUMAN FEEDING EXPERIMENTS

Experiments to influence lactase activity in man have been much fewer than experiments in animals. The first one reported was that of Cuatrecasas *et al.* in 1965¹¹⁷. Seven people with hypolactasia were given 150 g of lactose every day for 45 days without an increase in lactase activity being found. On the other hand, they observed a significant fall in lactose absorption in two subjects deprived of milk for five months. Knudsen *et al.*¹¹⁸ fed seven subjects with lactase persistence for the same time and the result was similar. In two subjects an increase of 25-40% was found, in three subjects the activity decreased by 50%, and the level remained unchanged in one subject. In two small experiments consisting of only two subjects⁷³ and one subject¹¹⁹ no change in jejunal lactase activity was observed after a lactose feeding of 10 and 14 days, respectively. A similar result was reported in a larger study in which 50 male Thais with hypolactasia were fed 50 g/day of lactose for 26 days¹²⁰. On the other hand, fasting was found to produce a fall in lactase activity¹²¹, but this was unspecific, because a decrease was observed in activities of other disaccharidases also.

As it was doubted whether human feeding experiments had been carried out for a sufficiently long period of time⁹¹, Kretchmer¹²², Gilat¹²³, and Gilat *et al.*¹²⁴ organised experiments lasting for six months and six to 14 months, respectively. Kretchmer could not increase lactose absorption ability in Nigerian medical students with hypolactasia, and Gilat *et al.* found no change in jejunal lactase activity in Jews even after a lactose feeding of one year. Chua and Seah reported similar results from Singapore¹²⁵. Other studies supported these findings¹²⁶⁻¹²⁷.

Besides these feeding experiments there was a good deal of information to suggest that lactose in the human diet does not prevent the appearance of hypolactasia in childhood or adolescence or, on the contrary, that the lack of lactose does not necessarily provoke the decline in lactase activity. There were observations that selective hypolactasia had developed even during the suckling period^{51,128} and in children who had drunk plenty of milk regularly after weaning⁵²⁻⁵³. Other subjects who had stopped milk drinking at weaning, but who had not developed hypolactasia, were also described^{54,129}. Flatz *et al.* found a Thai family¹²⁹ in which people had never drunk milk after weaning, and some family members had selective lactose malabsorption, while others did not. Quite recently Sahi and Launiala found four Finnish teenagers^{55,130} who had consumed a great deal of milk all their lives. At the age of 7, 10, 13, and 14 years they were lactose absorbers, while five years later they had

developed selective hypolactasia in spite of a regular milk consumption of two to five glasses a day.

FAMILY STUDIES

Some family studies were carried out because, at least in man, the genetic aetiology of the decline in jejunal lactase activity seemed to be more probable than the adaptive one. In 1965 Fischer and Zapf⁸¹ examined one family in which the mother and one of her two sisters had lactose malabsorption, but the father and two children were lactose absorbers. In 1967 Ferguson and Maxwell published a study concerning parents and six children¹³¹. Both parents and three of the children had a high level of lactase activity, two children having hypolactasia and one child having general malabsorption. Although the data were very limited, the authors put forward a hypothesis that a recessive autosomal single gene inheritance was involved. In 1968 Welsh *et al.*¹³² presented two Negro families in which both parents and all seven children were lactose malabsorbers and in 1970 two additional families in which all members were lactose malabsorbers⁵⁸. They also reported two white families in which one parent and some of the children had lactose malabsorption^{58,132}. In 1968 Neale¹³³ described a pedigree of an English family in which both parents were lactose absorbers, but one of the five children had lactose malabsorption. Flatz and Saengudom examined two families in Thailand¹²⁹. In both families the mother, one son and one daughter had lactose malabsorption, the others were lactose absorbers. No information was given about the possibility of the existence of general malabsorption, and blood glucose was determined only before and 30 minutes after the lactose load. Besides, Gudmand-Hoyer examined several families in Greenland^{134,135}, in some of which both parents and all children had lactose malabsorption. Ransome-Kuti *et al.*¹³⁶ studied 66 subjects in 13 Nigerian families and concluded that lactose absorption was transmitted by an incomplete dominant gene with sex dependency.

In 1973 Gilat *et al.*¹³⁷ published a large study consisting of 33 families and 167 people. In three families both parents were lactose absorbers. Two out of seven children in these three families had lactose malabsorption. In 11 families both parents had lactose malabsorption. In these families, 27 children had lactose malabsorption, and four were lactose absorbers. A regrettable drawback of this study was that the possible secondary origin of lactose malabsorption was not excluded.

The data in the families studied did not support dominant or recessive single gene inheritance given that the penetrance was complete. However, the bimodal distributions found in lactase activities⁷⁵ and glucose and galactose rises in lactose loading tests⁷⁹ suggested a single gene inheritance. When those persons in whom the selective nature of hypolactasia or lactose malabsorption was not confirmed were excluded from the families mentioned only five families remained^{58,131-132}. The distribution of selective hypolactasia in these families fitted the autosomal recessive single gene inheritance.

In 1973 and 1974 a large family study consisting of 338 subjects in 11 families was published in Finland^{54,84}. The diagnosis of hypolactasia was made based on the lactose loading test with ethanol and some biopsies. The possibility of secondary lactose malabsorption was excluded using a glucose-galactose loading test with ethanol. A careful genetic analysis showed that the distribution of selective hypolactasia in the pedigrees fitted excellently the

autosomal recessive single gene inheritance with complete penetrance. In addition, the observed prevalence of hypolactasia in the relatives of the probands was very close to the expected one that was calculated supposing the autosomal recessive inheritance.

Later Lisker *et al.* got similar results in Mexico¹³⁸. They examined 177 children in 61 families. The segregation of hypolactasia cases fitted well the autosomal recessive inheritance. Ransome-Kuti *et al.* studied 50 Nigerian children in 19 families and their results supported the same mode of inheritance¹³⁹.

Factors affecting decline in jejunal lactase activity

It seems conclusive that the decline in human jejunal lactase activity after infancy is genetically determined^{54,140} and the lack of dietary lactose plays perhaps no role or only a minor role. It is possible that abundant milk consumption delays the onset of hypolactasia^{53,55}. This may be supported by the fact that in countries where milk consumption is high in adulthood, as in Finland, the onset of hypolactasia is much later⁵³ than in countries where only a little milk is available even for children after infancy⁵². Findings in rats can be considered to support this conclusion¹⁰³.

The exact genetic mechanism which causes the late decline in lactase activity is not known. A question has arisen whether hormonal factors can influence the decline. It has been found that administration of glucocorticoids to suckling rats produces a precocious decline in the activity¹⁴¹, but they have no effect on the disaccharidase activities in the adult rat intestine¹⁴². Also adrenalectomy had no effect in adult rats¹⁴². Yeh and Moog¹⁴³ observed that hypophysectomy and thyroidectomy at 6 days of age prevented the normal decline in lactase activity. But when thyroxine was given activity decreased normally. Thus, thyroid hormone may play some part in the decline of lactase activity. Preliminary results show that the level of thyroxine in Finnish Lapps with hypolactasia was slightly higher than the level in people with lactase persistence¹⁴⁴.

The formation of human lactase may be influenced by three genes as in *Escherichia coli*¹⁴⁵. In congenital hypolactasia there may be a mutation in the structural gene for lactase, perhaps resulting in a total lack of synthesis or an incorrect and inactive enzyme. In the adult type it may be a mutation of the regulator gene or possibly the operator gene so that structurally normal lactase would be produced very slowly. Because the decline in lactase activity appears at an older age, it is possible that an additional (hormonal or other) factor is necessary to make the mutation apparent.

Two different lactases have also been postulated¹⁴⁶⁻¹⁴⁷. It is suggested that all except those people with congenital hypolactasia have an infant lactase, which then disappears and is replaced by an adult type. Those with congenital hypolactasia would develop adult lactase later. There is, however, no proof for this hypothesis. Recently Freiburghaus *et al.*¹⁴⁸ reported findings that the enzyme protein pattern in brush border membrane of jejunal epithelial cells in people with congenital and adult hypolactasia was very similar. They suggested that the mechanism resulting in congenital and adult hypolactasia is similar and they supported the idea of a regulatory defect in lactase synthesis.

If the problem of the genetic mechanism in congenital and adult hypo-

lactasia is to be solved, we have to improve techniques like those used by Freiburghaus *et al.*¹⁴⁸ to characterise lactase enzyme further. The definitive answer may, however, depend on the final isolation of brush border lactase. This has been a goal of investigators for a long time, but at present it is too difficult a task because of the lability of this enzyme.

More information is also needed about the factors that possibly predispose to hypolactasia, other than the genetic inheritance. Some attempts have already been made⁵⁵. Knowledge of those factors might elucidate why the decline in lactase activity manifests itself at different ages.

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